# Variability in Midlife Systolic Blood Pressure Is Related to Late-Life Brain White Matter Lesions
## The Honolulu-Asia Aging Study

Richard J. Havlik, MD; Daniel J. Foley, MS; Bryan Sayer, MHS; Kamal Masaki, MD;
Lon White, MD; Lenore J. Launer, PhD

***Background and Purpose***—Although white matter lesions (WMLs) on brain MRI in older persons are common, the mechanisms are unclear. Besides the associations with advanced age and high blood pressure (BP), variability in systolic BP (SBP) and the resulting changes in blood flow to the deep arteries of the brain may be contributing factors.

***Methods***—Japanese-American men in Hawaii have participated in a long-term study of cardiovascular disease, including midlife BP measurements at 3 clinical examinations in the period from 1965 to 1974. In the period from 1991 to 1993, dementia status was added to the fourth examination, and a brain MRI was completed in a fifth examination, which was from 1994 to 1996, on a subset of 575 men, who averaged 82 years. WMLs and ventricular atrophy were determined as the upper fifth in a standardized semiquantitative measure. Excess SBP variability was defined as greater than average increases in BP measurements from up to 3 examinations over 6 years. Logistic regression was used for the association of this variability with WMLs and atrophy, controlling for age, apolipoprotein E4 status, dementia diagnosis, and history of stroke.

***Results***—There were significant (2-fold) increased risks for WMLs among those with moderate and high SBP variability (third and fifth quintiles compared with the lowest quintile). Those in the highest SBP variability category (the fifth quintile) also had significantly more atrophy.

***Conclusions***—These SBP variability–MRI relationships suggest that variation in SBP in midlife may be a contributing factor to the development of WMLs and ventricular atrophy in late life. (***Stroke***. 2002;33:26-30.)

**Key Words:** blood pressure ■ epidemiology ■ magnetic resonance imaging ■ risk factors ■ white matter

White matter lesions (WMLs) in the brains of older persons are quite common and may result in clinical effects on cognition.[1] The etiology of these lesions include atherosclerotic risk factors, especially, elevated blood pressure (BP).[2–12] A frequently postulated mechanism is that hypertension affects the microcirculation of the brain in an adverse way, resulting in ischemia.[5] Most studies of BP and MRI are cross-sectional in design, or they are small clinical studies,[3,8,9] although there has been at least one longitudinal study.[9] In that study, it was noted that a U- or J-shaped relationship existed, with both lower and higher BPs being related to WMLs.[9] Also, cross-sectionally, there is a suggestion that postural hypotension might be associated with higher grade WMLs.[3] From these observations, BP variability, which has not been examined separately, may be affecting blood flow adversely, contributing to WMLs.[6,7]

The Honolulu-Asia Aging Study (HAAS) is a long-term longitudinal study of the effect of midlife cardiovascular and other risk factors on late-life outcomes of brain aging, including dementia and adverse findings on MRI.[13–15] Previously, systolic BP (SBP) variability over a period of 10 years was shown to be a predictor of the subsequent incidence of coronary heart disease in this population, even after correcting for BP level.[16] Such BP variability was hypothesized to be related to MRI findings.

## Subjects and Methods

The HAAS cohort was established in 1965 as the Honolulu Heart Program (HHP), a longitudinal epidemiological study of the risk factors for cardiovascular disease. The original cohort included 8006 Japanese-American men who were living on the Island of Oahu, Hawaii, and were aged 45 to 64 years when they were selected for baseline examination between 1965 and 1968. The initial study design and methods have been described in detail elsewhere.[17] The cohort was examined on 2 subsequent occasions after baseline in the periods 1968 to 1970 and 1971 to 1974; the examination included an ECG, which yielded heart rate measures. A follow-up visit of the

surviving cohort of 3734 men occurred in the period from 1991 to 1993 (examination 4) as part of the HAAS. At that time, an enhanced examination was administered that included cognitive testing and ascertainment of prevalent cases of dementia.[14] In the period from 1994 to 1996 (examination 5), cognitive status was retested, and incident dementia was ascertained. At examination 5, a sample received an MRI; selection criteria used age as well as cognitive, apolipoprotein E4 (apoE4), and stroke status.

Cognitive testing was performed at examinations 4 and 5 by use of the 100-point Cognitive Abilities Screening Instrument, which has elements of the Hasegawa Dementia Scale, the Mini-Mental State Examination, and the Modified Mini-Mental State Examination.[18] Those individuals meeting education-adjusted screening criteria had a more extensive neurological and cognitive examination at a follow-up visit. Adequate data were acquired to allow the application of the criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (edition 3, revised) for the diagnosis of dementia. Further differentiation of Alzheimer's disease from vascular dementia was ascertained by a consensus panel using standard criteria.[14]

ApoE genotyping was performed according to recognized procedures in the laboratory of the Bryan Alzheimer's Disease Research Center at Duke University.[19] Individuals were classified as apoE4 positive if they had at least 1 E4 allele (E24, E34, or E44); other genotypes (E32, E33, and E22) were grouped as E4 negative. Other information concerning age, education, and antihypertensive drug use was acquired by standard questionnaires. Information on the presence of stroke through 1993 came from an ongoing hospital surveillance system of the HHP that used multiple sources to acquire information and to complete a consensus diagnosis.

A subsample of men underwent MRI of the brain.[15] The brain MRI subsample was chosen by use of information from examinations 4 and 5. In addition to an ≈10% random sample of those participating in examination 5, there was an oversampling of those with prevalent dementia (excluding the severely demented, who might not be able to undergo the procedure), those with possible dementia, those with apoE4 genotype, those with clinical stroke, and those at the oldest ages. Originally, 845 men were invited for the procedure. Because of deaths, refusals, technical difficulties, and other reasons, 599 MRI scans were sent to the Central Reading Center (71% response rate), and 575 had an MRI that could be processed successfully for all relevant variables. Those with successful scans, compared with those in the total sample selected for MRI, were younger and were less likely to be demented or to have had a stroke, but they had a higher percentage of apoE4 positivity (33% versus 24%, respectively). The participants and readers were unaware of their apoE status. The protocols and procedures were approved by the institutional review committee of the Kuakini Medical Center. Informed consent was obtained from those receiving the MRI, including information about the procedure and the plan to inform them about any clinically relevant abnormalities.

### MRI End Points
Brain MRI was completed at the Kuakini Medical Center, Honolulu, Hawaii, with use of a GE Signa Advantage 1.5-T machine. The protocol required ≈20 to 30 minutes and included 4 sequences: (1) sagittal 5-mm sections, (2) a 3D oblique spoiled-gradient recalled-echo sequence with 124 slices of 1.6 mm, (3) axial proton density–weighted fast spin-echo sequence, and (4) axial fast spin-echo sequence (T2-weighted, 3-mm sections). By use of visual standards, semiquantitative readings for WMLs and ventricular size, both on a scale of 0 to 9, were performed at the Central Reading Center at Johns Hopkins University, according to a protocol first developed for the Cardiovascular Health Study (CHS).[20] The end point for WMLs was set at grades 5 to 9 (mild or greater confluence of WMLs in the periventricular or broader regions), and for atrophy, it was set at grades 6 to 9 (borderline or definite increase in ventricular volume).

### BP Measures
BPs were measured at each examination in a comparable manner after the participant sat for ≈10 minutes. They were taken by use of

**TABLE 1.  Characteristics of MRI Population: HAAS (575 Subjects)**

| Characteristics of Subjects | |
| --- | --- |
| Late life | |
| Mean±SD age,* y | 81.6±5.0 |
| apoE4,* % | 35.8 |
| Dementia,*† % | 21.4 |
| Stroke,† % | 12.2 |
| Grades 5–9 WMLs,* % | 18.4 |
| Grades 6–9 ventricular atrophy,* % | 23.0 |
| Midlife | |
| <12 y of education,‡ % | 56.7 |
| Smoking habit,§ % | 25.0 |
| Use of alcohol,§ % | 71.0 |
| Mean±SD SBP,‡ mm Hg | 132.3±16.3 |
| Mean±SD diastolic BP,‡ mm Hg | 82.8±9.3 |
| BP treatment,§ % | 22.6 |

*1994–1996; †1991–1993; ‡1965–1974; and §1971–1974.

a mercury sphygmomanometer with a standard cuff, except at the fourth examination, when appropriately sized cuffs were used. Diastolic BP was determined by the disappearance of Korotkoff sounds. Up to 3 BPs were taken at examinations 1 and 2, and up to 2 BPs were taken at examination 3. When >1 BP reading by either a physician or a nurse was available, the mean for each reader was used. Otherwise, the single physician's reading and the single nurse's reading were used in computing variability. BP from examination 4 was not used in the assessment of variability, and a single mean, regardless of reader, was computed for additional analyses. Pulse pressure was defined as the difference between SBP and diastolic BP.

### Statistical Analysis
For participants in the MRI study, the mean SBP measurements for the first 3 exams, which covered a 6-year period of follow-up, were regressed on the subject's age (in years) at each examination. From the individual's regression line, the slope represents the average change in BP per year of age, and the variation of the observed data around the predicted regression line represents midlife variability over the 6 years. To quantify the midlife variation, we used the mean squared error, ie, the variance of the residuals from each person's regression model. This approach is similar to a previous analysis of variability completed in the HHP population.[16] A similar approach was used to assess heart rate variability. Orthostatic hypotension was measured at examination 4 and defined as a drop in SBP of ≥20 mm Hg or in diastolic BP of ≥10 mm Hg from the supine to the standing position after 3 minutes.[21]

In the analysis of outcomes, the total midlife SBP variation was divided into quintiles, and the quintiles were entered as individual dummy variables, with the lowest quintile (least variability) used as the reference group. In addition to variability, the slope (average individual change in SBP per year of age) and the average systolic midlife BP were included in the analysis. Logistic regression was used to estimate the odds ratios of being in an MRI subgroup thought to be associated with substantial brain damage. A similar atrophy end point had been used in a previous analysis from this population.[15]

## Results
The sample was quite old (mean 82 years). Because of sampling, there was a relatively higher percentage of demented, apoE4-positive, and stroke cases compared with the total cohort. Of the selected MRI subgroups, 18.4% exhibited WMLs, and 23% exhibited ventricular atrophy (Table 1).

**TABLE 2.   Multivariate Analysis of Midlife SBP Characteristics and WMLs (Grades 5–9) and MRI Atrophy (Grades 6–9)**

|  | WML* | | Atrophy* | |
|---|---|---|---|---|
|  | Odds Ratio | CL | Odds Ratio | CL |
| Midlife mean SBP | 1.01 | 0.99–1.02 | 0.99 | 0.98–1.01 |
| SBP slope with midlife age | 1.09 | 1.01–1.18 | 0.97 | 0.90–1.04 |
| BP treatment (examinations 1–3) | 1.18 | 0.66–2.10 | 1.45 | 0.84–2.50 |
| SBP variability 2† | 1.62 | 0.73–3.60 | 1.87 | 0.92–3.81 |
| SBP variability 3 | 2.27 | 1.08–4.79 | 1.68 | 0.84–3.38 |
| SBP variability 4 | 1.98 | 0.92–4.26 | 1.38 | 0.67–2.85 |
| SBP variability 5 | 2.20 | 1.01–4.79 | 2.70 | 1.32–5.52 |

CL indicates confidence limit.

*Adjusted for age, education, apoE4, stroke, and dementia.

†Compared with least variability (quintile 1).

Midlife characteristics were similar to the midlife characteristics of those survivors not undergoing an MRI. The mean SBP variability was 92 mm Hg, with a standard deviation of 166 mm Hg, and ranged from 1 to 896 mm Hg. The SBP variability quintile cut points from lowest to highest were as follows: 30, 51, 81, and 133.

In Table 2, the SBP slope (ie, the rate of increase in SBP with age at the 3 examinations) was associated with more WMLs. Midlife mean SBP and BP treatment were not associated with WMLs in these multivariate analyses. Compared with the lowest quintile, the upper 3 quintiles of SBP variability were elevated in risk for WMLs; significance was reached for the third and fifth quintile. Exclusion of those receiving BP treatment (23%) did not result in a substantial change in the results; however, because of the smaller sample size, the odds ratios for the fifth quintile became nonsignificant, and the second quintile became significant, suggesting some instability of the estimates. Cerebral atrophy was associated with extreme variability (ie, the highest quintile compared with the lowest quintile). There was no relationship with diastolic BP variability, pulse pressure, or heart rate variability (not shown).

At examination 4, elevated SBP (fifth quintile versus first quintile) measured 1 to 3 years before the MRI was associated with frequent WMLs (odds ratio 2.09, confidence limit 1.00 to 4.37) but not atrophy. There was no relationship of either MRI end point with orthostatic hypotension assessed at examination 4.

## Discussion

The findings in the present study indicate that midlife SBP variability is associated with WMLs detected in late-life MRIs. The most extreme level of BP variability is also associated with atrophy. The mechanism for these relationships is unknown; however, a possible explanation involves the chronic occurrence of periods of higher and lower SBP levels, which overcome the autoregulation maintaining blood flow in the cranial vessels. This variation could result in periods of relative ischemia in vulnerable areas. Such an explanation is consistent with the fact that the deeper white matter tissues are supplied by terminal vessels in the brain and lack sufficient anastomoses with other vessels. Such tissues might be at higher risk from SBP variation.[7] These circumstances could result in the development of small brain lesions seen on MRI and described in pathological material.

In a previous analysis predicting coronary heart disease and including 4 examinations in the same population over a period of 10 years, it was estimated that the mean SBP variance was ≈110 mm Hg, with a standard deviation of 160 mm Hg, suggesting fairly wide swings in BP in some participants.[16] In the subset included in the present analysis, BPs from only 3 examinations were used and covered 6 years. Consequently, the variability was slightly less, but substantial (≈90 mm Hg, with a standard deviation of 160 mm Hg). Because of a 15-year gap between examinations 3 and 4, we chose not to include this measure in estimating BP variability and examined its effects separately.

Another factor is the mechanism of the BP variability. It has been reported that some individuals react adversely to having their BP performed by a physician, and the resulting BP increase results in so-called "white coat hypertension."[22] Studies in such individuals with the use of 24-hour BP monitoring suggest that in a substantial proportion, this is a transient phenomenon and may not be a long-term risk factor for WMLs, stroke, or coronary disease. The more at-risk individuals are likely to be a separate subgroup in whom the BP variability is a harbinger of the subsequent onset of more fixed elevations of SBP. The differentiation of these subgroups might allow earlier and more appropriate SBP therapy and avoid longer term consequences. Also, age-associated SBP elevations, which are associated with decreased arterial compliance, could be a factor. However, pulse pressure, another indication of vascular stiffness, was not related to the MRI findings. In the previous analysis of SBP variability and subsequent coronary heart disease incidence, the untreated group was at particular risk.[16] When the treated group was excluded in this study, the results were similar. However, in a more contemporary study of hypertensive treatment, certain drugs seemed to be associated with more WMLs than others, suggesting the need to clarify which are the most appropriate treatment modalities.[23]

Although the emphasis of this analysis is on midlife BP variability and its probable later adverse effects, there is increasing evidence of possible acute effects on the brain from BP variability in elderly hypertensive patients. It has been suggested that in these patients the threshold of BP that is required to maintain flow may be at a higher setting.[23] So, for example, periods of relative hypotension occurring with sleep could compound any existing brain involvement. Additional evidence comes from a study of WMLs in demented patients who had assessments of postural hypotension and possible carotid sinus sensitivity. Those with the greatest BP drops had increased severity of MRI-detected WMLs.[24] However, postural hypotension measured ≈3 years before the MRI was not a significant predictive factor in the present study.

Another issue in the interpretation of the results of this analysis is the functional significance of the presence of WMLs. WMLs have been considered in some studies as a benign concomitant of aging and in other studies as evidence

of substantial brain pathology, especially of an ischemic nature.[2] Recent cross-sectional studies[3] and follow-up studies[9] support the latter "damage" view and have suggested increased risk for the onset of dementia, cognitive impairment, and stroke as well as difficulty in walking and other outcomes, including death.[1,26] In addition, there have been correlations found between MRI findings of WMLs and pathological examination of the same brains, with the conclusion that the WMLs represent areas of ischemia in the myelin that are very similar to lacunes in the gray matter. These have been characterized as "incomplete" white matter infarction because they are pathologically without complete necrosis and cystic formation. There are similarities of these lesions to other ischemic lesions in the brain, which are found near strokes or lacunes. In addition, when detailed studies are performed for association between MRI on postmortem brains and pathology, more arteriosclerosis has been noted in vessels in the areas of the pathological lesions.[2] Thus, there is strong evidence that vascular changes are an underlying link between BP and WMLs. One explanation is that vessels become more tortuous and longer because of arteriosclerosis. This pathology raises the minimal BP threshold necessary to sustain perfusion. So, it is possible that in these cases, even normal BP would be inadequate to maintain blood flow, with the resulting formation of MRI pathology.

WMLs were quite common in this elderly Japanese-American population, as has been shown in other community samples.[3,9] Our sample was enriched with men at greater risk for WMLs because of the presence of dementia, apoE4, and stroke. There were ≈18% with grade 5 or greater lesions compared with only ≈7% in the CHS population.[3] Also, the HAAS population was older and consisted only of men of Japanese ancestry. Overlap of WMLs with atrophy of the brain was found in 8.5% in this population versus an expected overlap of only 4% if these features were independent, probably because of associated brain pathology. It is also possible that a common etiologic agent, such as hypertension, would affect both WMLs and the frequency of stroke, leading to atrophy. This atrophy is probably the summation of a number of processes destructive to brain tissue.

There are inconsistencies in some of the other observed relationships in the present study compared with other studies. For example, the midlife BP itself is not an independent predictor of MRI outcome, although at the more recent examination, from 1991 to 1993, the subgroup of those with SBP in the highest quintile had significantly more WMLs; this finding was similar to findings in Rotterdam and of the CHS.[3,9] This lack of association might be the result of selective mortality from the adverse effects of hypertension, which could distort some of the long-term relationships. Also, more frequent use of BP therapy later in life may have diminished some of the adverse effects. At examination 3, antihypertensive therapy was received by ≈20% of participants, but 20 years later, the frequency was >40%.[14]

The present study has some limitations that should be kept in mind when evaluating the results. The participants receiving the MRI were a small proportion of the original cohort, and power to detect relationships was limited. There were likely other selection biases beyond those used in adjusting the results, and these could have affected the results. Although great care was taken in avoiding missing data and measurement error, there is still the possibility of bias. The various BP measures were interrelated to a certain extent, and this colinearity could have affected the results. The generalizability to women, other race/ethnic groups, or to other locations should be done with caution. Finally, the data are observational in nature with known limitations.

In conclusion, the results of the present study provide probable new insights into the mechanisms of WML formation. It appears that such lesions are related not only to the level of SBP but also to its variability. It will be important to attempt to duplicate these results in other longitudinal long-term studies. Also, in terms of mechanistic studies, interdisciplinary investigations with hypertensive-prone animals might be used to clarify some of the possible processes affecting these brain changes. Because further epidemiological and animal studies are indicated to clarify the reported relationships, the practical clinical ramifications are not clear at this time.

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